

Psychophysiological Hypotheses Regarding Multiple Chemical Sensitivity Syndrome

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This paper proposes several hypotheses and research strategies for exploring possible psychological factors contributing to multiple chemical sensitivity (MCS). The hypotheses are based on concepts of individual response stereotypy, situational response specificity, classical conditioning of chemical-induced responses, and psychophysiological reactions to active and passive coping orientations. Hypotheses regarding hypersensitivity to perception and/or aversiveness of chemical stimulation also are presented. Strategies for evaluating these hypotheses are described based on experimental literature on psychophysiology and psychophysics. — *Environ Health Perspect* 105(Suppl 2):479–483 (1997)

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Introduction

The topic of psychological aspects of multiple chemical sensitivity syndrome (MCS) raises some political issues, particularly with individuals who have the disorder and resent being treated as if the problem were imaginary. Therefore, before the topic can be addressed scientifically, some justification sensitive to these concerns must be made for undertaking this avenue of investigation. I propose the following.

First, conducting research on possible psychological or psychophysiological contributions to MCS does not imply that MCS is entirely or primarily psychological. Scientific investigation is neutral on the topic. If psychological factors play no role or a minimal role in MCS, a program of good research will be able to establish this firmly. If psychological factors do play a part, then understanding them can only

help in the prevention and treatment of this debilitating problem.

Second, if psychological factors are found to play an important role in MCS, this does not necessarily imply that the problem is imaginary. The distinction between psychological and somatic disorders has become blurred in recent years. It is well known that psychological factors can exacerbate a variety of somatic diseases, including headache (1–3), ischemic heart disease (4), cancer (5,6), Raynaud's disease (7), rheumatoid arthritis (8), asthma (9), irritable bowel syndrome (10), chronic pain (11), and even some infectious diseases (12). The role of psychological factors in exacerbation of these diseases has been firmly established. Some evidence also exists for a possible contributing role in diathesis.

Conversely, some psychological disorders are known to be triggered by physical ailments that produce similar symptoms. For example, panic disorder and other anxiety disorders have a statistical relationship with the presence of such disorders as mitral valve prolapse (13), hyperthyroidism (14), irritable bowel syndrome (15,16), and asthma (17,18). Although no firm evidence exists regarding the direction of causality, several theories have been proposed implicating these physical disorders as causal factors in panic disorder. Also, psychological disorders including anxiety and depression have been linked to particular kinds of brain pathology, such as depressed levels of serotonin and

various structural abnormalities (19,20). So even some purely psychological disorders have physiological bases. If a chemical exposure adversely affects the central nervous system, some of the resulting symptoms may look like mental disorders.

Third, finding an important role for psychological procedures in treating MCS does not necessarily exclude the possibility that the disorder is organic in origin. This is true even if these psychological procedures are as effective or more effective than various medical interventions. For example, this is the case for muscle contraction (21) and migraine headaches (22,23), irritable bowel syndrome (24,25), and Raynaud's disease (26). Psychological components in treatment programs have proven effective for hypertension (27), cancer (28,29), and epilepsy (30), to name a few. If exposure to chemicals is a psychological stressor among MCS patients (probably in addition to being a physical trigger of symptoms), a stress-related autonomic reaction also may occur, perhaps superimposed on other physical reactions.

This paper reviews some of the psychophysiological research paradigms that have been used to describe human psychophysiological response to various kinds of stimulation. If neuropsychological factors play any role in MCS, their influence may be measured by research using some of these paradigms.

Psychophysiological Concepts As Applied to MCS

Individual Response Stereotypy

Research from the 1950s to the 1970s shows that some individuals tend to produce highly specific physiological responses to many stressors whereas others apparently do not. This tendency has been called individual response stereotypy (31). Thus, some people respond primarily with heart rate (HR) variability, or just with skin conductance responses, to a variety of psychological challenges, from mental arithmetic to scary movies to reaction time tasks. Individuals who respond in one physiological system may not respond in another.

Not everyone shows individual response stereotypy, but some do to a marked extent. It has been hypothesized that in some cases stereotypy may predispose an individual to psychosomatic disease (32). Consistent with this, individuals with family histories of hypertension (and who therefore may

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Abbreviations used: CNS, central nervous system; HR, heart rate; MCS, multiple chemical sensitivity.

have a physiological predisposition to hypertension) tend to show greater cardiovascular reactivity to a variety of laboratory stressors (33). Similarly, asthmatics have been found to react to a variety of stressors with bronchoconstriction (34) and muscle contraction headache patients react with tension in the skeletal muscles of the face and shoulders, etc. (35). It is possible that severe chemical exposure may act as an unconditional stimulus, producing one-trial learning of a conditioned neuropsychological response. It may have a particular sensitizing effect upon individuals who are predisposed to stereotypic psychophysiological responsiveness (e.g., in the lung or the nose) even before exposure. Later this same physiological response may generalize and be elicited by other substances. In this stage it may also be elicited in response to psychological stressors.

In some people response to chemical exposure may be in the cardiovascular system (palpitations, faintness), in some cases in the respiratory system (wheezing or mucous secretions), and in some cases such chemical exposure may cause nausea, inflammation, fever, fatigue, muscular aches and pains, weakness, or perhaps psychological symptoms such as confusion, anxiety, or depression. After chemical exposure, it is possible that the body's self-regulatory system is compromised, so exposure to various kinds of stressors, particularly chemical ones, produces a stereotyped physiological stress response in this subpopulation. To the extent that this response may be mediated in part by the central nervous system (CNS), psychological factors may be involved.

Situational Response Specificity

Some tasks elicit characteristic physiological responses (31). For example, tasks eliciting an attitude of active coping tend to produce a particular response characterized by beta sympathetic activation: increased heart rate and systolic blood pressure, bronchodilation, and increased ventilation (36–39). Aversive tasks associated with a more passive response (e.g., watching a scary film) tend to elicit responses such as alpha sympathetic activation (peripheral vasoconstriction), increased cardiotropic parasympathetic activity, and bronchoconstriction (40–42).

If exposure to chemicals is a psychological stressor among MCS patients (in addition to possibly being a physical trigger of symptoms), a stress-related autonomic reaction also may occur, perhaps superimposed on other physical reactions. If exposure

cannot be avoided, we might expect the psychological component of the response to be similar to the passive coping profile: faintness, increased vagal tone, and asthma-like symptoms. On the other hand, if the individual finds the exposure situation aversive and can avoid it, the response may include rapid heartbeat and perhaps palpitations, bronchodilation, and increased ventilation. These all are common symptoms in MCS. According to this theory, however, if the situation is not perceived to be aversive, no observable autonomic response is expected except that directly produced by the chemical (which should be observable in people without MCS and in lower animals).

There is also evidence that exposure to stimuli previously associated with chemical exposure can produce a strong conditioned psychophysiological response specific to the particular chemical (43). Siegel has hypothesized that this response is adaptive in that it may prepare the body for dealing with oncoming chemical exposure more effectively (43). Thus, as observed in everyday situations, the sight and smell of food elicits various changes in the gastrointestinal tract. Aromas, sights, and sounds associated with a particular place immediately elicit thoughts and often feelings and desires. Perfume elicits such powerful emotional responses that major industries have been capitalizing for centuries on pronounced psychophysiological effects of chemicals in the air. It is possible that through psychological conditioning such exposures might also elicit physiological reactions that could explain at least some of the symptoms of MCS.

Some specific symptoms of disease can even be triggered by suggestion. In the asthma literature a number of studies have provided evidence that psychogenic asthma attacks can occur even when a person simply thinks that exposure to an asthma trigger has occurred. The typical experimental paradigm here involves telling the asthmatic subject that (s)he is being exposed to an asthma trigger (an allergen or a bronchoconstrictor), and then subjecting the person to a convincing exposure of an inert substance (e.g., nebulized saline or just room air); the subject believes that (s)he has been exposed to a nebulized bronchoconstrictor. Among some asthmatics (between 1 in 4 and 1 in 20, depending on the study), a clinically significant bronchoconstriction occurs (34). Similarly, bronchodilation may occur in some subjects when they believe they are being exposed

to a bronchodilator (44). Clinically significant bronchoconstriction responses tend not to occur in nonasthmatics, although brief and small but statistically significant responses sometimes occur in this group as well. (45).

Relationship between Individual Response Stereotypy, Stimulus Response Specificity, and Psychosomatic Disease

It is possible that psychosomatic disease may occur when a person with a tendency toward individual response stereotypy is repeatedly exposed over long periods of time to situations that also specifically evoke that person's characteristic response. Under such circumstances, the body may change its homeostatic set point, or it may continually return to a level of physiological arousal that may be maladaptive in other respects. Alternatively, the organism may become overly sensitized to particular types of stimulation and thus may overreact to stimulation that ordinarily would evoke no response. Such sensitization may occur either after repetitive stimulation or even after a single mass exposure, as in traumatic conditioning, particularly where the organism is preprogrammed to develop such a response. The concept of biological prepotency or preparedness has been used to describe the tendency for certain biologically relevant stimuli to be more powerful than others as nonhabituating and/or conditional stimuli (46). Although biological prepotency does not explain much variance in development of human phobias, as originally hypothesized (47) it is possible that certain types of chemical stimulation may be found to be prepotent in this way. Thus, we might hypothesize that MCS patients, whose systems are highly attuned to cues of chemical exposure, show a similar psychophysiological sensitization to olfactory cues of chemical exposure after repeated or traumatic exposure. The critical factor distinguishing such reactions from nonpsychological sensitization reactions (e.g., as may occur in allergies) is the role of the central nervous system and psychological experience in producing the effects.

Effects of Cognitive Style

Research on coping with stress suggests that the cognitive orientation of the individual toward stressful stimulation has a measurable and reliable effect on physiological response (48). It is reasonable, therefore, to hypothesize that this is also true when stimulation is in the form of

aversive chemical exposure. Some individuals may interpret chemical exposure as aversive, unavoidable, and inescapable, and thus exhibit a passive coping response. In such cases, symptoms of faintness and dyspnea may prevail because of increased vagal tone and bronchoconstriction. Others may experience palpitations and discomfort associated with muscle tension, because they experience the stimulation as a "call to action." Still others may not consider exposure aversive, and so exhibit no emotionally induced physiological response.

Differences in Perceptual Sensitivity for Olfactory Stimulation

Because the presence and severity of MCS are determined primarily by self-reporting of symptoms, it is possible that sensitivity and ability (or willingness) to report unpleasant sensations are important components of the clinical presentation of the disease. Therefore it is important to study the sensitivity of MCS patients to various kinds of body stimulation and compare it to the sensitivity of individuals without this problem. Greater perceptual sensitivity to the magnitude or aversiveness of chemical stimulation would be consistent with the possibility that MCS is mediated, in part, by psychophysiological processes, although this would not prove definitively that such processes have a causal role. The keenness of perception of olfactory stimulation may be a particularly important variable. This may be measurable using any of several paradigms in psychophysics (49).

Magnitude Estimation

Magnitude estimation would involve exposing MCS patients to various quantities of inhaled chemicals and then asking them to rate the relative magnitude of the exposures. This can be done by asking patients to give a number proportional to the amount of exposure relative to a standard stimulus of exposure. The usual metric associated with this method is the slope of the gain in perception of intensity relative to the gain in actual exposure. Individuals who are more sensitive to stimulation would have higher slopes, usually after data are converted to a log-log function, to account for the expected curvilinearity in all modes of perception.

In addition, the aversiveness associated with exposure can be quantified. Based on previous research on pain and on asthma, it would be useful to measure relevant dimensions of the chemical-induced symptoms.

It is known that most physical symptoms have two independent dimensions: intensity and unpleasantness. Of these, the intensity dimension tends to be more closely related to physical intensity of stimulation, whereas unpleasantness is related to the subject's emotional reaction to the stimulation. These two dimensions have been documented in laboratory studies of experimentally induced pain (50) and dyspnea (51). Tursky et al. (50) developed the Pain Perception Profile, a verbal rating scale for psychophysical estimate of pain. We have adapted it for assessment of dyspnea in asthma (51). If MCS individuals experience greater discomfort than others but similar levels of perception, this provides some evidence that central nervous system centers involving emotional reactivity (e.g., limbic centers) are sensitized in this population or perhaps that endorphin levels, which may mitigate feelings of discomfort, are particularly low in this population. If sensitivity to the magnitude of the stimulation is elevated among MCS patients, it is possible that sensory nerves and reflexes associated with sensation may be more active among MCS patients. Data from our laboratory suggest that psychological factors may have a greater impact on perception of the unpleasantness of a stimulation than in perception of the magnitude or intensity of the stimulus (52).

Threshold Detection

Another method for quantifying perceptual sensitivity to stimulation is threshold detection. In this procedure the intensity of exposure is gradually increased to the point at which the individual first feels something. This point is the threshold of detection. Threshold detection studies also can determine the threshold for detecting a "just noticeable difference" in exposure. If MCS patients have lower absolute and difference thresholds than other subjects, it is possible that they are more tuned to reacting to this type of stimulation. Differences in sensitivity may reflect either physiological processes (e.g., greater sensory receptor sensitivity) or psychological processes (e.g., greater alertness to chemical stimulation). A single study by Doty et al. (53) found no differences between MCS patients and normal individuals in the threshold for detecting the odor of phenyl ethyl alcohol and methyl ethyl ketone, but throughout the testing session MCS patients were found to have higher nasal resistances, respiration rates, and Beck Depression inventory scores. These data suggest that MCS

patients may not be perceptually more sensitive to odors than other subjects, but they generally exhibit greater depression and decreased nasal patency.

Method of Production

Instead of responding verbally in threshold detection tasks, individuals can self-administer stimulation and stop the stimulation when they have reached a threshold of detection. This method can be used in conjunction with the magnitude estimation method; i.e., subjects can estimate the magnitude of discomfort. In one study, our laboratory used this method with patients suffering from muscle contraction headaches (54). A tourniquet was tied around their upper arms and subjects were asked to pump a ball until they began to feel discomfort, then pain, then pain sufficient to make them want to stop pumping. (To prevent subjects from harming themselves they were not permitted to do this task for more than 1.5 min.) We found that headache patients detected discomfort and pain within shorter time periods than other subjects but reported the pain to be more intense than did the other subjects. This suggested that headache pain patients were more sensitive than others to forms of ischemic pain in areas other than the head.

Hyperventilation as a Possible Intervening Variable in MCS

Many physical and emotional stressors produce hyperventilation, as do some disease states involving pulmonary or renal dysfunction. Symptoms of hyperventilation are extraordinarily varied, and can include some common symptoms of MCS. They can include headache, dyspnea, palpitations, tremor, pain, panic, and even seizure activity (55). It would therefore be of interest to study the occurrence of hyperventilation in this population, particularly in response to chemical stimulation. If hyperventilation plays a role in MCS, then the respiratory responses of MCS victims may be expected to differ from those of normal subjects and may be more similar to those among people with known respiratory abnormalities or panic disorder, both of which produce measurable effects on respiratory response to stress.

A tendency to hyperventilate can be measured noninvasively by measuring end-tidal CO₂ via a small tube placed at the end of the nostril. A decrease in petCO₂ might be expected after chemical exposure among individuals who hyperventilate and may indicate an emotional response to

such stimulation. Although the existence of such a response would not indicate that the symptoms of MCS are necessarily caused by a hyperventilation response (because correlation cannot prove causation), lack of correlation could rule out stimulus-induced hyperventilation as a mediating variable in MCS.

In addition to petCO₂, other respiratory measures may provide useful information. Measures of respiratory resistance can assess responses involving bronchodilation or bronchoconstriction. Bronchodilation may predispose a person to hyperventilate, whereas bronchoconstriction may produce some asthmalike symptoms. If MCS patients react bronchially more to psychological stress than other individuals, it is possible that this response may contribute to some of the symptoms of MCS.

Assessing respiratory drive after exposure to various chemical stressors also would assess the possibility of an augmented

respiratory response. Asthmatics tend to show a greater increase in inspiratory effort in response to breathing through external resistors than do other individuals, and panic disorder patients show greater inspiratory pressure responses in response to breathing CO₂. If MCS patients show greater increases in respiratory drive than others when exposed to noxious chemicals, this would also suggest that some symptoms of MCS may result from hyperventilation.

Conclusion

This paper has presented some paradigms that have proven useful in the field of psychophysiology, and which have shed some light on asthma and panic disorder. Similar research also has revealed information about the contribution of psychological factors to hypertension and cardiovascular disease as well as to a host of other ailments. Finding an association between MCS and psychophysiological responsivity

does not necessarily prove a relationship, but it may produce useful information about the mechanisms of MCS that could prove important in finding treatments for the disorder. For example, if hyperventilation were associated with MCS, then breathing retraining programs may be helpful. If heightened perceptual sensitivity is involved, desensitization paradigms may be helpful. If differences in interpretation of physical stimulation are involved, cognitive therapy may play a role, as may some antianxiety medication. If a passive coping orientation is implicated, alternative strategies might be explored that involve helping individuals develop more active strategies to cope with various physical and emotional stressors. Psychophysiological investigation of MCS, therefore, holds promise of detecting factors that may help in psychological control symptoms and consequent reduction in disability.

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